Docket No.: HMSU-P11-006
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Ingham et al.

#44
B.G.J
12/4/02

Application No.: 08/954771 Group Art Unit: 1646

Filed: October 20, 1997 Examiner: M. Brannock

For: VERTEBRATE EMBRYONIC PATTERN-INDUCING PROTEINS AND USES RELATED THERETO

SUBMISSION OF FORMAL DRAWINGS

Commissioner for Patents
Washington, DC 20231

Dear Sir:

Submitted herewith is one set (nineteen sheets, sixteen figures) of formal drawings for filing in the above-identified patent application. Kindly substitute the enclosed formal drawings for the informal drawings submitted with the originally filed application.

Applicants believe no fee is due other than the fees for filing a CPA. However, if an additional fee is due, please charge our Deposit Account No. 18-1945, under Order No. HMSU-P11-006 from which the undersigned is authorized to draw.

Dated: November 15, 2002

Respectfully submitted,

By

David P. Halstead, Ph.D.
Registration No.: 44,735
ROPES & GRAY
One International Place
Boston, Massachusetts 02110-2624
(617) 951-7000
(617) 951-7050 (Fax)
Attorneys for Applicant

```
DROSOPHILA HEDGEHOG     RCKEKLNVLAYSVMNEWPGIRLLVT
CHICKEN HEDGEHOG-A      RCKERVNSLAIAVMHMWPGVRLRVT
CHICKEN HEDGEHOG-B      RCKDKLNALAISVMNQWPGVKLRVT

DROSOPHILA HEDGEHOG     ESWDEDYHHGQESLHYEGRAVTIAT
CHICKEN HEDGEHOG-A      EGWDEDGHHLPDSLHYEGRALDITT
CHICKEN HEDGEHOG-B      EGWDEDGHHSEESLHYEGRAVDITT

DROSOPHILA HEDGEHOG     SDRDQSKYGMLARLAVEAGFDWV
CHICKEN HEDGEHOG-A      SDRDRHKYGMLARLAVEAGFDWV
CHICKEN HEDGEHOG-B      SDRDRSKYGMLARLAVEAGFDWV
```

Fig. 1

```
1   ---------------------------------------- CHICKEN SONIC HEDGEHOG
1   MDNHSSVPWASAASVTCLSLDAKCHSSSSSSSSKSAASSI DROSOPHILA HEDGEHOG

1   ------------------MVEMLLLTRILLVGFICALLVS CHICKEN SONIC HEDGEHOG
41  SAIPQEETQTMRHIAHTQRCLSRLTSLVALLLIVLPMVFS DROSOPHILA HEDGEHOG

23  SGLTCGPGRGIGKRRHPKKLTPLAYKQFIPNVAEKTLGAS CHICKEN SONIC HEDGEHOG
81  PAHSCGPGRGLGRHR-ARNLYPLVLKQTIPNLSEYTNSAS DROSOPHILA HEDGEHOG

63  GRYEGKITRNSERFKELTPNYNPDIIFKDEENTGADRLMT CHICKEN SONIC HEDGEHOG
120 GPLEGVIRRDSPKFKDLVPNYNRDILFRDEEGTGADRLMS DROSOPHILA HEDGEHOG

103 QRCKDKLNALAISVMNQWPGVKLRVTEGWDEDGHHSEESL CHICKEN SONIC HEDGEHOG
160 KRCKEKLNVLAYSVMNEWPGIRLLVTESWDEDYHHGQESL DROSOPHILA HEDGEHOG

143 HYEGRAVDITTSDRDRSKYGMLARLAVEAGFDWVYYESKA CHICKEN SONIC HEDGEHOG
200 HYEGRAVTIATSDRDQSKYGMLARLAVEAGFDWVSYVSRR DROSOPHILA HEDGEHOG

183 HIHCSVKAENSVAAKSGGCFPGSATVHLEHGGTKLVKDLS CHICKEN SONIC HEDGEHOG
240 HIYCSVKSDSSISSHVHGCFTPESTALLESGVRKPLGELS DROSOPHILA HEDGEHOG

223 PGDRVLAADADGRLLYSDFLTFLDRMDSSRKLFYVIETRQ CHICKEN SONIC HEDGEHOG
280 IGDRVLSMTANGQAVYSEVILFMDRNLEQMQNFVQLHT-D DROSOPHILA HEDGEHOG

263 PRARLLLTAAHLLFVAPQHNQSEATGSTSGQALFASNVKP CHICKEN SONIC HEDGEHOG
319 GGAVLTVTPAHLVSVWQ-------PESQKLTFVFADRIEE DROSOPHILA HEDGEHOG

303 GQRVYVLGEGGQQLLPASVHSVSLREEASGAYAPLTAQGT CHICKEN SONIC HEDGEHOG
352 KNQVLVRDVETGELRPQRVVKVG-SVRSKGVVAPLTREGT DROSOPHILA HEDGEHOG

343 ILINRVLASCYAVIEEHSWAHWAFAPFRLAQGL---LAA- CHICKEN SONIC HEDGEHOG
391 IVVNSVAASCYAVINSQSLAHWGLAPMRLLSTLEAWLPAK DROSOPHILA HEDGEHOG

379 --LCPDGAIPTAATTTTGIHWYSRLLYRIGSWVLDGDALH CHICKEN SONIC HEDGEHOG
431 EQLHSSPKVVSSAQQQNGIHWYANALYKVKDYVLPQSWRH DROSOPHILA HEDGEHOG

417 PLGMVAPAS                                 CHICKEN SONIC HEDGEHOG
471 D                                         DROSOPHILA HEDGEHOG
```

Fig. 2

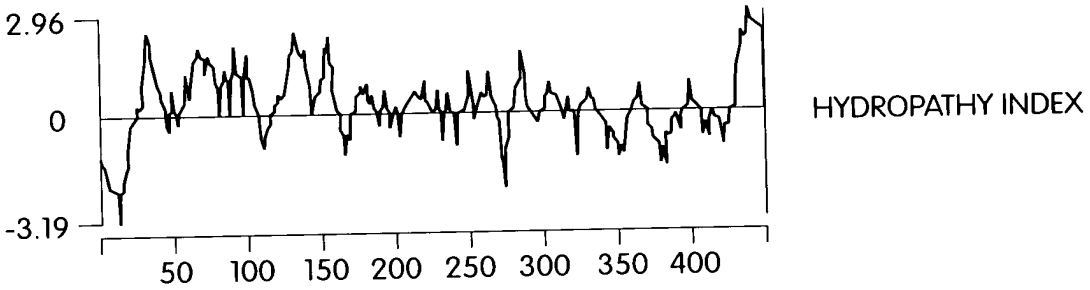

Fig. 3

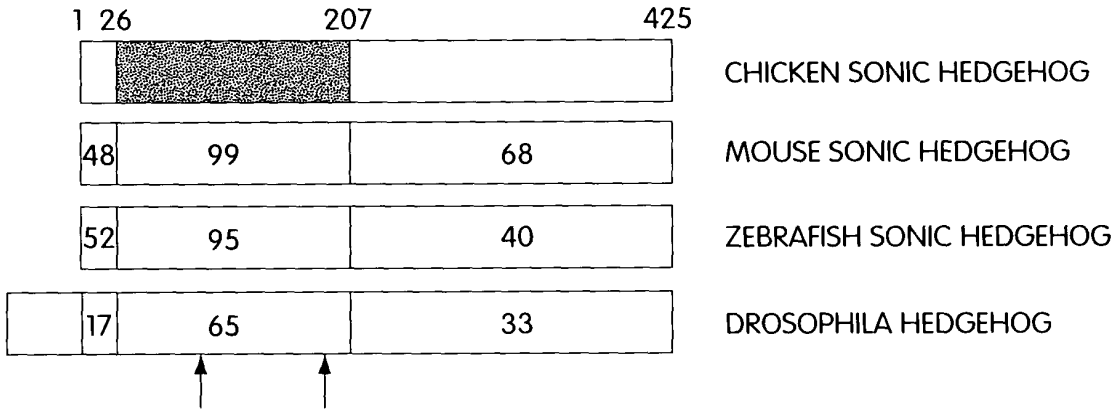

Fig. 4

```
                1
D-hh    MDNHSSVPWA  SAASVTCLSL  DAKCHSSSSS  SSSKSAASSI  SAIPQEETQT
M-Dhh   ..........  ..........  ..........  ..........  ..........
M-Ihh   ..........  ..........  ..........  ..........  ..........
M-Shh   ..........  ..........  ..........  ..........  ..........
C-Shh   ..........  ..........  ..........  ..........  ..........
Z-Shh   ..........  ..........  ..........  ..........  ..........

               51                           Y
D-hh    MRHIAHTQRC  LSRLTSLVAL  LLIVLPMVFS  PAHSCGPGRG  LGRHR...AR
M-Dhh   ..........  ..MALPASLL  PLCCLALLAL  SAQSCGPGRG  PVGRRRYVRK
M-Ihh   ..........  ..........  ..........  ..........  ..........
M-Shh   ..........  MLLLLARCFL  VILASSLLVC  PGLACGPGRG  FGKRRH..PK
C-Shh   ........MV  EMLLLTRILL  VGFICALLVS  SGLTCGPGRG  IGKRRH..PK
Z-Shh   ..........  .MRLLTRVLL  VSLLTLSLVV  SGLACGPGRG  YGRRRH..PK

              101
D-hh    NLYPLVLKQT  IPNLSEYTNS  ASGPLEGVIR  RDSPKFKDLV  PNYNRDILFR
M-Dhh   QLVPLLYKQF  VPSMPERTLG  ASGPAEGRVT  RGSERFRDLV  PNYNPDIIFK
M-Ihh   ..........  ..........  ..........  ...ERFKELT  PNYNPDIIFK
M-Shh   KLTPLAYKQF  IPNVAEKTLG  ASGRYEGKIT  RNSERFKELT  PNYNPDIIFK
C-Shh   KLTPLAYKQF  IPNVAEKTLG  ASGRYEGKIT  RNSERFKELT  PNYNPDIIFK
Z-Shh   KLTPLAYKQF  IPNVAEKTLG  ASGRYEGKIT  RNSERFKELT  PNYNPDIIFK

              151
                    Y
D-hh    DEEGTGADRL  MSKRCKEKLN  VLAYSVMNEW  PGIRLLVTES  WDEDYHHGQE
M-Dhh   DEENSGADRL  MTERCKERVN  ALAIAVMNMW  PGVRLRVTEG  WDEDGHHAQD
M-Ihh   DEENTGADRL  MTQRCKDRLN  SLAISVMNQW  PGVKLRVTEG  RDEDGHHSEE
M-Shh   DEENTGADRL  MTQRCKDKLN  ALAISVMNQW  PGVRLRVTEG  WDEDGHHSEE
C-Shh   DEENTGADRL  MTQRCKDKLN  ALAISVMNQW  PGVKLRVTEG  WDEDGHHSEE
Z-Shh   DEENTGADRL  MTQRCKDKLN  SLAISVMNHW  PGVKLRVTEG  WDEDGHHFEE

              201
D-hh    SLHYEGRAVT  IATSDRDQSK  YGMLARLAVE  AGFDWVSYVS  RRHIYCSVKS
M-Dhh   SLHYEGRALD  ITTSDRDRNK  YGLLARLAVE  AGFDWVYYES  RNHIHVSVKA
M-Ihh   SLHYEGRAVD  ITTSDRDRNK  YGLLARLAVE  AGFDWVYYES  KAHVHCSVKS
M-Shh   SLHYEGRAVD  ITTSDRDRSK  YGMLARLAVE  AGFDWVYYES  KAHIHCSVKA
C-Shh   SLHYEGRAVD  ITTSDRDRSK  YGMLARLAVE  AGFDWVYYES  KAHIHCSVKA
Z-Shh   SLHYEGRAVD  ITTSDRDKSK  YGTLSRLAVE  AGFDWVYYES  KAHIHCSVKA

              251
                Y
D-hh    DSSISSHVHG  CFTPESTALL  ESGVRKPLGE  LSIGDRVLSM  TANGQAVYSE
M-Dhh   DNSLAVRAGG  CFPGNATVRL  RSGERKGLRE  LHRGDWVLAA  DAAGRVVPTP
M-Ihh   EHSAAAKTGG  CFPAGAQVRL  ENGERVALSA  VKPGDRVLAM  GEDGTPTFSD
M-Shh   ENSVAAKSGG  CFPGSATVHL  EQGGTKLVKD  LRPGDRVLAA  DDQGRLLYSD
C-Shh   ENSVAAKSGG  CFPGSATVHL  EHGGTKLVKD  LSPGDRVLAA  DADGRLLYSD
Z-Shh   ENSVAAKSGG  CFPGSALVSL  QDGGQKAVKD  LNPGDKVLAA  DSAGNLVFSD

              301
D-hh    VILFMDRNLE  QMQNFVQLHT  .DGGAVLTVT  PAHLVSVWQ.  ......PESQ
M-Dhh   VLLFLDRDLQ  RRASFVAVET  ERPPRKLLLT  PWHLVFAAR.  ...GPAPAPG
M-Ihh   VLIFLDREPN  RLRAFQVIET  QDPPRRLALT  PAHLLFIADN  HTE....PAA
M-Shh   FLTFLDRDEG  AKKVFYVIET  LEPRERLLLT  AAHLLFVAP.  HNDSGPTPGP
C-Shh   FLTFLDRMDS  SRKLFYVIET  RQPRARLLLT  AAHLLFVAPQ  HNQSEATGST
Z-Shh   FIMFTDRDST  TRRVFYVIET  QEPVEKITLT  AAHLLFVLDN  STEDLHTMT.
```

Fig. 5A-1

```
          351
D-hh      KLTFVFADRI  EEKNQVLV..  RDVETGELRP  QRVVKVG.SV  RSKGVVAPLT
M-Dhh     DFAPVFARRL  RAGDSVLA..  ..PGGDALQP  ARVARVA.RE  EAVGVFAPLT
M-Ihh     HFRATFASHV  QPGQYVLV..  ..SGVPGLQP  ARVAAVS.TH  VALGSYAPLT
M-Shh     S..ALFASRV  RPGQRVYVVA  ERGGDRRLLP  AAVHSVTLRE  EEAGAYAPLT
C-Shh     SGQALFASNV  KPGQRVYVLG  E..GGQQLLP  ASVHSVSLRE  EASGAYAPLT
Z-Shh     ...AAYASSV  RAGQKVMVVD  DSGQLKSVIV  QRIYT....E  EQRGSFAPVT
          401
D-hh      REGTIVVNSV  AASCYAVINS  QSLAHWGLAP  MRLLSTLEAW  LPAKEQLHSS
M-Dhh     AHGTLLVNDV  LASCYAVLES  HQWAHRAFAP  LRLLHALGAL  LP........
M-Ihh     RHGTLVVEDV  VASCFAAVAD  HHLAQLAFWP  LRLFPSL...  ..........
M-Shh     AHGTILINRV  LASCYAVIEE  HSWAHRAFAP  FRLAHALLAA  LAPARTDGGG
C-Shh     AQGTILINRV  LASCYAVIEE  HSWAHWAFAP  FRLAQGLLAA  LCP.......
Z-Shh     AHGTIVVDRI  LASCYAVIED  QGLAHLAFAP  ARLYYYVSSF  LSP.......
          451
D-hh      PKVV......  ...SSAQQQN  GIHWYANALY  KVKDYVLPQS  WRHD*
M-Dhh     ..........  ...GGAVQPT  GMHWYSRLLY  RLAEELMG*
M-Ihh     ..........  .AWGSWTPSE  GVHSYPQMLY  RLGRLLLEES  TFHPLGMSGA
M-Shh     GGSIPAAQSA  TEARGAEPTA  GIHWYSQLLY  HIGTWLLDSE  RMHPLGMAVK
C-Shh     DGAIPTA...  .....ATTTT  GIHWYSRLLY  RIGSWVLDGD  ALHPLGMVAP
Z-Shh     KTPAVGPMRL  YNRRGSTGTP  GSC......H  QMGTWLLDSN  MLHPLGMSVN
          501
M-Ihh     GS*
M-Shh     SS*
C-Shh     AS*
Z-Shh     SS*
```

Fig. 5A-2

```
M-Dhh:  CGPGRGPVGRRRYVRKQLVPLLYKQFVPSMPERTLGASGPAEGRVTRGSERFRDLV
M-Ihh:  ************************************************ERFKELT
H-Ihh:  ************************************************
H-Shh:  CGPGRGFGKRRH**PKKLTPLAYKQFIPNVAEKTLGASGRYEGKISRNSERFKELT
C-Shh:  CGPGRGIGKRRH**PKKLTPLAYKQFIPNVAEKTLGASGRYEGKITRNSERFKELT
M-Shh:  CGPGRGFGKRRH**PKKLTPLAYKQFIPNVAEKTLGASGRYEGKITRNSERFKELT
Z-Shh:  CGPGRGYGRRRH**PKKLTPLAYKQFIPNVAEKTLGASGRYEGKITRNSERFKELT
CON:    CGPGRGXXRRXXXPKXLXPLXYKQFXPXXXEXTLGASGXXEGXXXRXSERFXXLT

        PNYNPDIIFKDEENSGADRLMTERCKERVNALAIAVMNMWPGVRLRVTEGWDEDGH
        PNYNPDIIFKDEENTGADRLMTQRCKDRLNSLAISVMNQWPGVKLRVTEGRDEDGH
        ******************RRLMTQRCKDRLNSLAISVMNQWPGVKLRVTEGWDEDGH
        PNYNPDIIFKDEENTGADRLMTQRCKDKLNALAISVMNQWPGVKLRVTEGWDEDGH
        PNYNPDIIFKDEENTGADRLMTQRCKDKLNALAISVMNQWPGVKLRVTEGWDEDGH
        PNYNPDIIFKDEENTGADRLMTQRCKDKLNALAISVMNQWPGVRLRVTEGWDEDGH
        PNYNPDIIFKDEENTGADRLMTQRCKDKLNSLAISVMNHWPGVKLRVTEGWDEDGH
        PNYNPDIIFKDEENXGADRLMTXRCKXXXNXLAISVMNXWPGVXLRVTEGXDEDGH

        HAQDSLHYEGRALDITTSDRDRNKYGLLARLAVEAGFDWVYYESRNHIHVSVKAD
        HSEESLHYEGRAVDITTSDRDRNKYGLLARLAVEAGFDWVYYESKAHVHCSVKSE
        HSEESLHYEGRAVDITTSDRDRNKYGLLARLAVEAGFDWVYYESKAHVHCSVKSE
        HSEESLHYEGRAVDITTSDRDRSKYGMLARLAVEAGFDWVYYESKAHIHCSVKAE
        HSEESLHYEGRAVDITTSDRDRSKYGMLARLAVEAGFDWVYYESKAHIHCSVKAE
        HSEESLHYEGRAVDITTSDRDRSKYGMLARLAVEAGFDWVYYESKAHIHCSVKAE
        HFEESLHYEGRAVDITTSDRDKSKYGTLSRLAVEAGFDWVYYESKAHIHCSVKAE
        HXXXSLHYEGRAXDITTSDRDXXKYGXLXRLAVEAGFDWVYYESXXHXHXSVKXX
```

Fig. 5B

	M-Dhh	M-Ihh	C-Shh	Zf-Shh	D-hh
M-Shh	61 (77)	63 (78)	84 (92)	68 (80)	48 (64)
M-Dhh		58 (75)	61 (77)	54 (71)	51 (68)
M-Ihh			64 (78)	61 (75)	48 (68)
C-Shh				68 (80)	49 (64)
Zf-Shh					47 (64)

Fig. 6

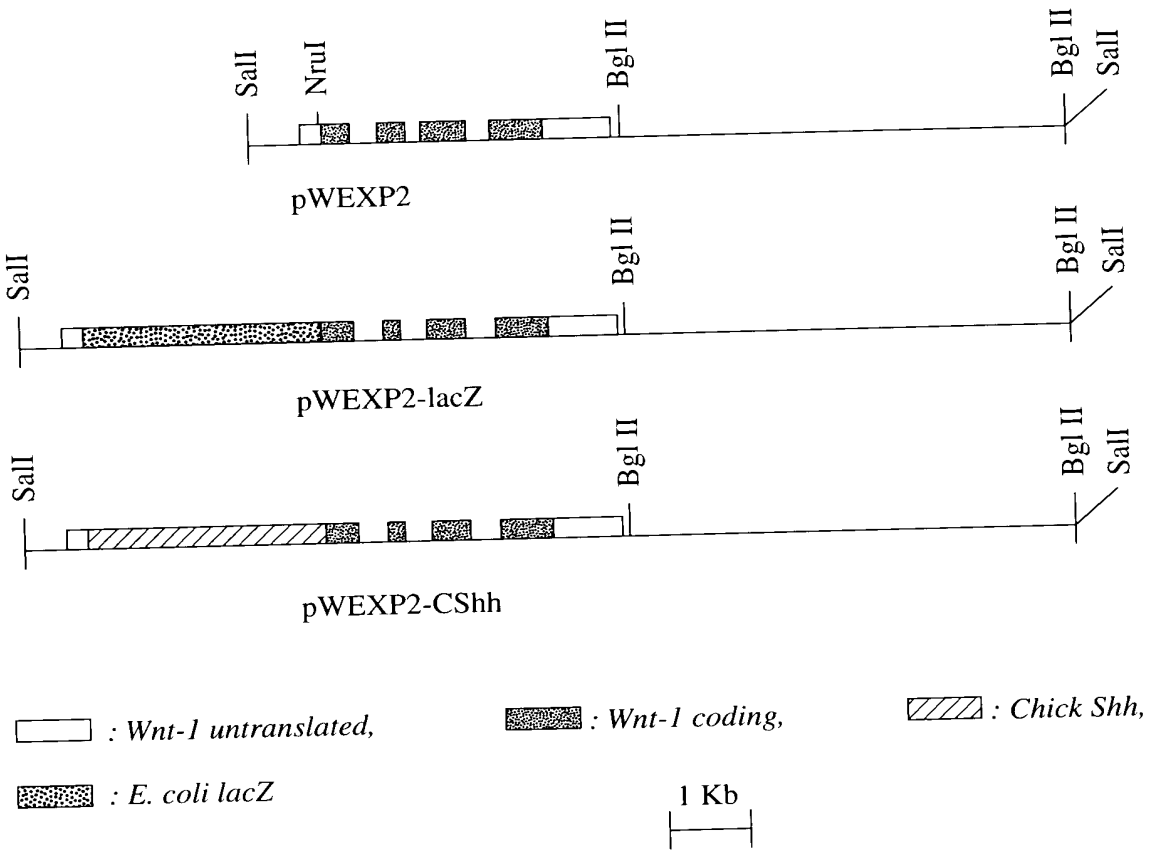

Fig. 7

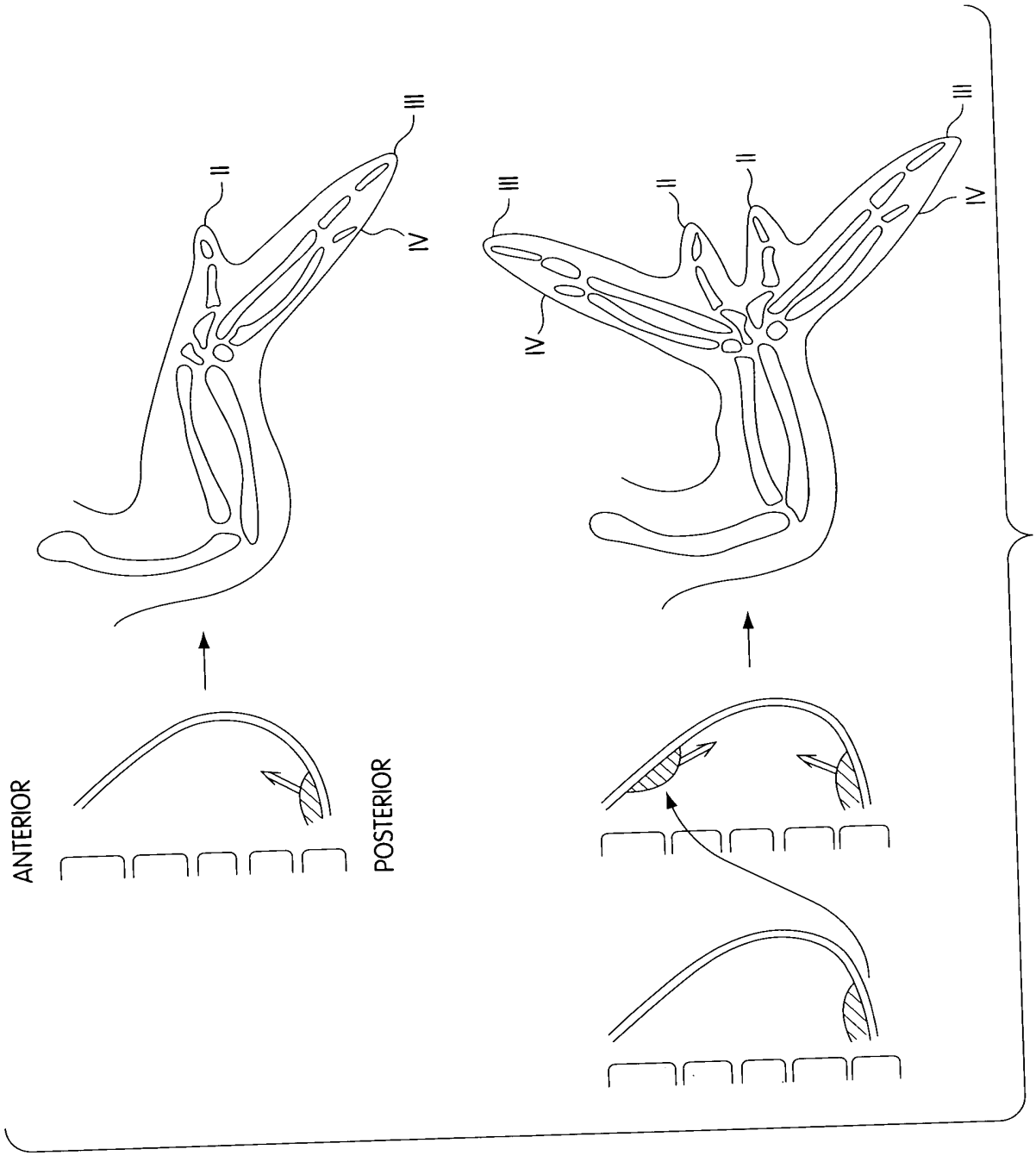

Fig. 8

```
 hh   1   MDNHSSVPWASAASVTCLSLDAKCHSSSSSSSSKSAASSISAIPQEETQT

shh       ..................................................

 hh  51   MRHIAHTQRCLSRLTSLVALLLIVLPMVFSPAHSCGPGRGLGRHR.ARNL
                      ||      |  |  | |    ||||||  ||  |    |
shh   1   ..........MRLLTRVLLVSLLTLSLVVS.GLACGPGRGYGRRRHPKKL

 hh 100   YPLVLKQTIPNLSEYTNSASGPLEGVIRRDSPKFKDLVPNYNRDILFRDE
           ||  ||  |||  |  |  |||  ||  |  |  |  ||  |  ||||  ||  |  ||
shh  40   TPLAYKQFIPNVAEKTLGASGRYEGKITRNSERFKELTPNYNPDIIFKDE

 hh 150   EGTGADRLMSKRCKEKLNVLAYSVMNEWPGIRLVVTESWDEDYHHGQESL
           |  |||||||  |||  |||  ||  ||||  |||  |  |||  ||||  ||  |||
shh  90   ENTGADRLMTQRCKDKLNSLAISVMNHWPGVKLRVTEGWDEDGHHFEESL

 hh 200   HYEGRAVTIATSDRDQSKYGMLARLAVEAGFDWVSYVSRRHIYCSVKSDS
           |||||||  |  ||||||  ||||  |  ||||||||||||  |  |  ||  ||||
shh 140   HYEGRAVDITTSDRDKSKYGTLSRLAVEAGFDWVYYESKAHIHCSVKAEN

 hh 250   SISSHVHGCFTPESTALLESGVRKPLGELSIGDRVLSMTANGQAVYSEVI
           |  |||  |  |  |  |  |  |  ||  ||  |  |  |  |
shh 190   SVAAKSGGCFPGSALVSLQDGGQKAVKDLNPGDKVLAADSAGNLVFSDFI

 hh 300   LFMDRNLEQMQNFVQLHT.DGGAVLTVTPAHLVSVWQPESQKL...TFVF
           |  ||  |  |  |  |  |  |||  |  |  |
shh 240   MFTDRDSTTRRVFYVIETQEPVEKITLTAAHLLFVLDNSTEDLHTMTAAY

 hh 347   ADRIEEKNQVLVRDVETGELRPQRVVKVGSVRSKGVVAPLTREGTIVVNS
           |  |  |  |  |  |  |  ||  |  |||||
shh 290   ASSVRAGQKVMVVD.DSGQLKSVIVQRIYTEEQRGSFAPVTAHGTIVVDR

 hh 397   VAASCYAVINSQSLAHWGLAPMRLLSTLEAWLPAKEQL.....HSS
           |||||||  |  |||  ||  ||  |  |  |
shh 339   ILASCYAVIEDQGLAHLAFAPARLYYYVSSFLSPKTPAVGPMRLYNRRGS

 hh 438   PKVVSSAQQQNGIHWYANALYKVKDYVLPQSWRHD 471
           |  |  |  |  |
shh 389   TGTPGSCHQMGTWLLDSNMLHPLGMSV..... 415
```

Fig. 9A

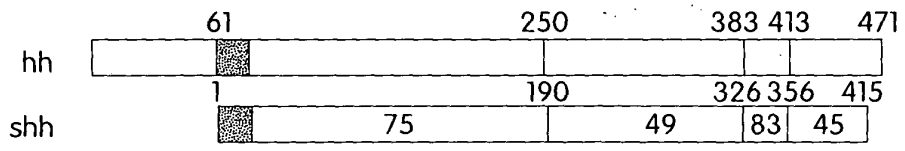

Fig. 9B

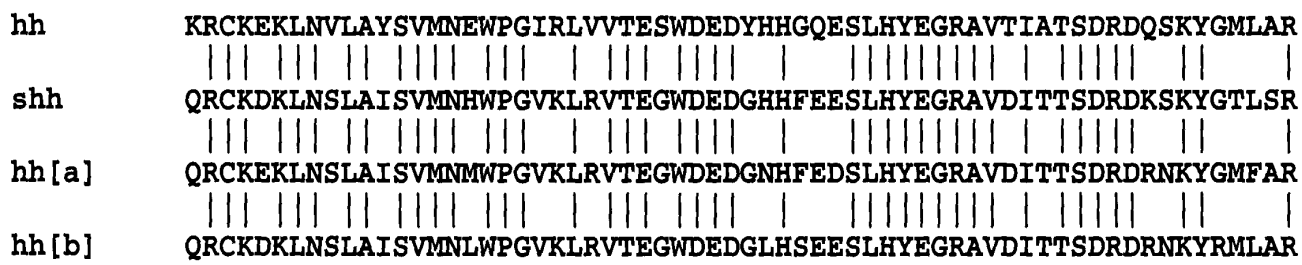

Fig. 10

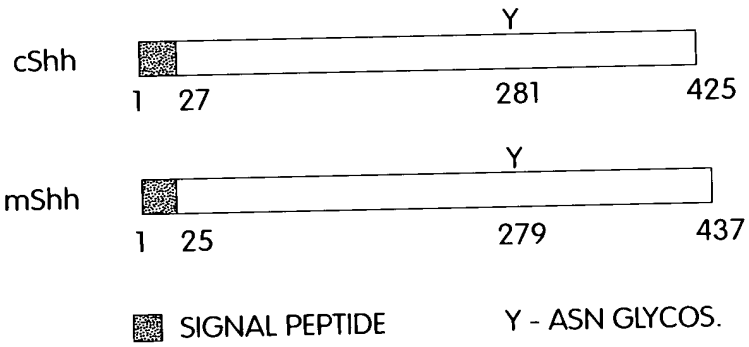

Fig. 11

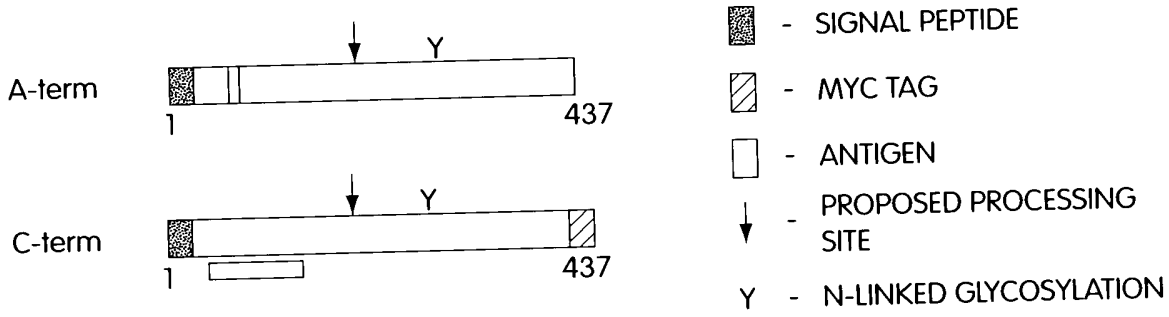

Fig. 12

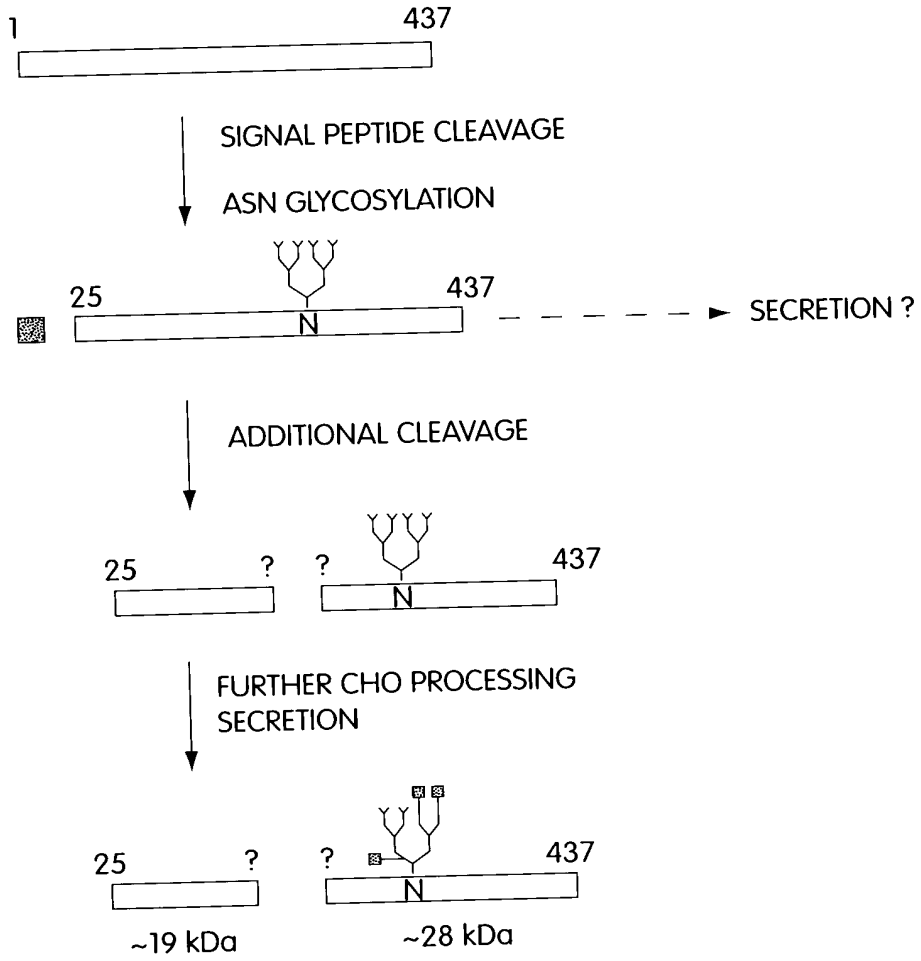

Fig. 13

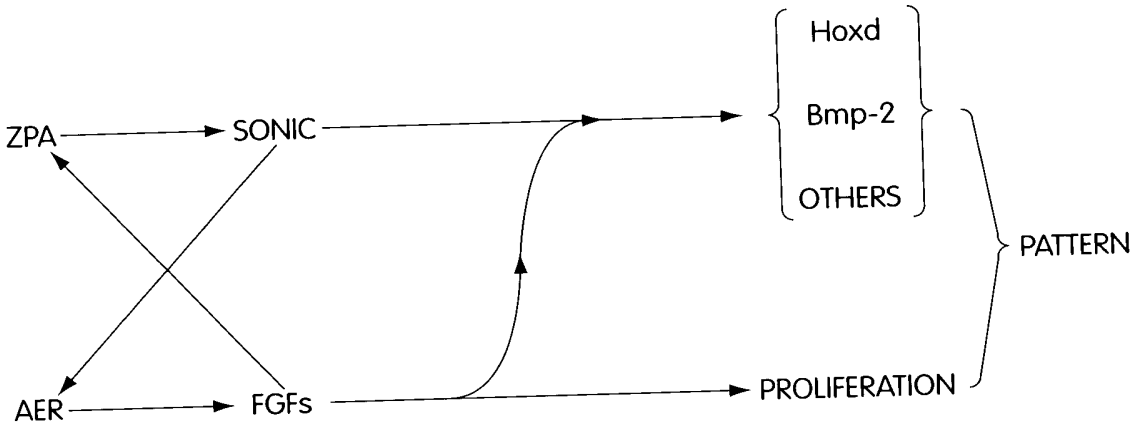

Fig. 14

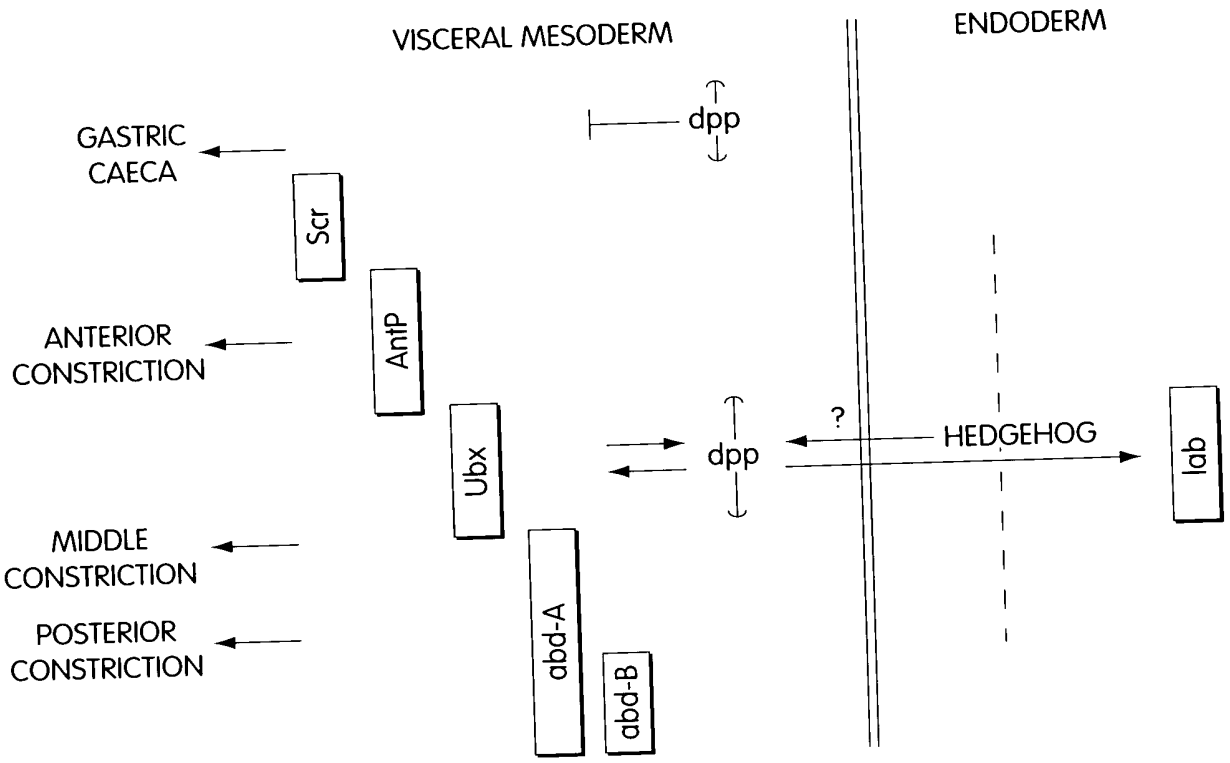

Fig. 15A

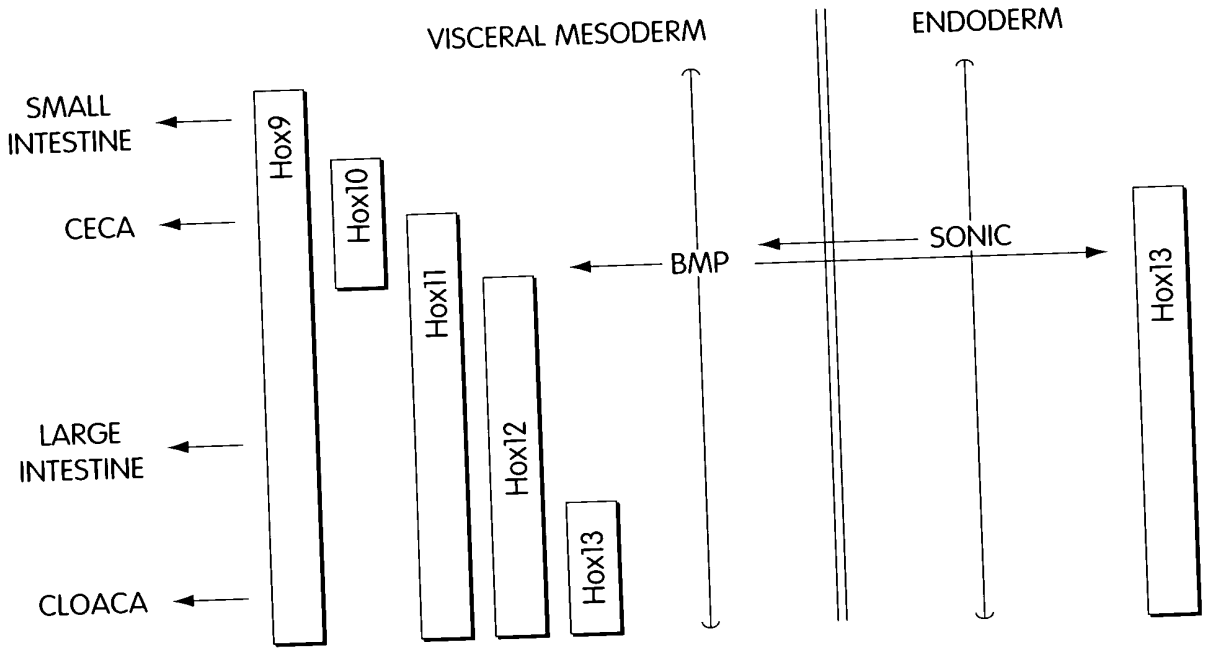

Fig. 15B

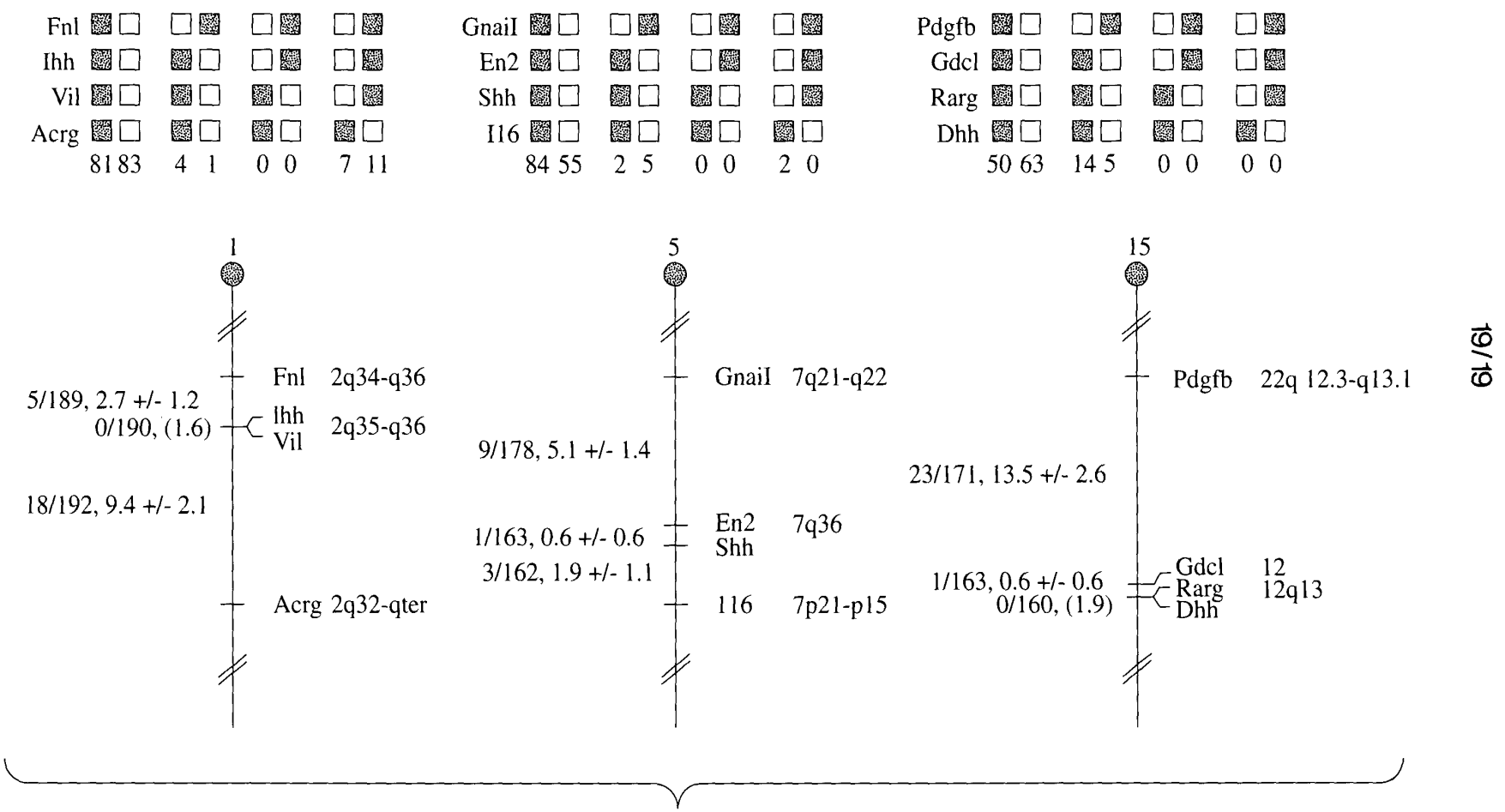

Fig. 16